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Original article

Dynamic changes in specific anti-L-asparaginase antibodies generation during acute lymphoblastic leukemia treatment

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ABSTRACT

Background: L-asparaginase (L-asp) remains one of the key components of acute lymphoblastic leukemia therapy. Immune reactions to the drug are associated with its diminished activity. The aim of the study was to determine the level of IgM, IgG and IgE-class anti-L-asp antibodies during the induction and reinduction phases of acute lymphoblastic leukemia therapy and their influence on L-asp activity.
Methods: The study group comprised 65 patients treated for acute lymphoblastic leukemia in one pediatric oncology center. L-asp antibodies were assessed using ELISA at the end of the induction and reinduction phases. L-asp activity was assessed prior to each drug administration by colorimetry.
Results: At the end of the first exposure to L-asp antibodies were detected in 35 patients (54%). In the reinduction phase of the treatment anti-L-asp antibodies were found in 38/55 patients (69%). In the induction phase patients with inadequate L-asp activity had higher IgM concentrations (median 5.88 *versus* 2.81 μg/mL, $p = 0.03$). In the reinduction phase IgG and IgM levels correlated inversely with L-asp activity. Patients with L-asp allergy had higher levels of IgG (median 61.6 *versus* 18.36 μg/mL, $p = 0.01$), whereas higher IgE levels were noted in the group of patients with inadequate drug activity (median 0.91 *versus* 0.64 μg/mL, $p = 0.03$).
Conclusions: Subsequent exposure to L-asp in the treatment of acute lymphoblastic leukemia was associated with the increase of anti-L-asp antibodies in all studied classes. However, the changes observed in specific classes of antibodies were not distinctive for L-asp hypersensitivity or inactivation, suggesting that the mechanism is more complex.

Introduction

L-asparaginase (L-asp) is a bacteria-derived hydrolase that has been the basis for the treatment of acute lymphoblastic leukemia (ALL) for more than fifty years. L-asp (EC 3.5.1.1) degrades asparagine into aspartic acid and ammonia [1]. Its antileukemic properties derive from the fact that lymphoblasts are characterized by low asparagine synthetase activity, and therefore are dependent on the extracellular content of asparagine [2]. In an asparagine-depleted environment, leukemia cells undergo defective protein synthesis and undergo processes of programmed cell death [3].

The clinical efficacy of the drug is limited by the development of anti-L-asp-specific antibodies, which is associated with diminished L-asp activity [4,5]. The development of the antibodies is usually accompanied by the occurrence of hypersensitivity reactions [6].The clinical symptoms of L-asp allergy vary from local manifestations to systemic reactions; they usually occur in patients re-exposed to the drug in reinduction/intensification protocols, and may affect up to 60% of patients [5,7]. The immunogenicity of L-asp depends on the formulation of the drug, its route of administration and phase of treatment. Some subsets of patients may experience inadequate L-asp activity without displaying clinical symptoms of hypersensitivity, a phenomenon known as 'silent inactivation'. Most of these patients have anti-L-asp antibodies, although some of them may be antibody-

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negative [8]. This suggests the existence of another mechanism responsible for reduced L-asp activity.

The great majority of studies assessing the properties of anti-L-asp antibodies evaluate IgG immunoglobulins. Their role in L-asp therapy has been well established, although the results of studies assessing their influence on overall survival have been conflicting [5,6,9]. Our previous report highlighted an association between anti-L-asp IgM class antibodies, L-asp activity and outcome [10]. The role of IgE antibodies in L-asp hypersensitivity and inactivation remains unclear [11,12]. The fact that a significant proportion of immune reactions against L-asp occur during the first minutes of drug administration suggests a significant degree of involvement by mast cell degranulation, and the release of histamine and other inflammatory mediators; this indicates the process is IgE-dependent. Furthermore, the presence of IgE-class antidrug antibodies (ADA) is typically associated with clinically overt allergy, whereas inactivation of the enzyme mainly depends on specific IgG antibodies [13,14].

The aim of our study was to assess the development of IgM, IgG and IgE-class anti-L-asp antibodies in the induction and reinduction protocols of ALL treatment and their influence on L-asp activity.

Materials and methods

Patients and drug administration

The research protocol was approved by the local Ethics Committee, and informed consent was obtained from all participants, or their legal representatives where appropriate. The study group comprised 65 children (33 boys) aged 0.5–17 years, who were receiving treatment in a single pediatric oncology center for *de novo* diagnosed acute lymphoblastic leukemia. In the study group, 55 children were classified as standard or intermediate risk patients (SR + IR), and 10 were classified as high-risk patients (HR). The leukemia treatment protocol was based on the Berlin-Frankfurt-Munster (BFM) therapeutic strategy. During the induction phase of the treatment, all patients (n = 65) received native *E. coli*-asparaginase (Asparaginase, Medac GmbH, Germany) at a dose of 5000 U/m^2 on days 12, 15, 18, 21, 24, 27, 30 and 33. However, as the further stages of L-asp treatment differed between the SR + IR and HR groups (HR group received additional courses of high-dose L-asp prior reinduction) only patients in the SR + IR group were selected for further analysis (n = 55). These patients in the reinduction protocol received a second L-asparaginase course at a dose of 10 000 U/m^2 on days 8, 11, 15 and 18. In each patient, a 1 mL blood sample was collected for activity assessment, prior to the administration of each dose of the drug, except for the first doses given on day 12 of induction and day 8 of reinduction. Anti-L-asp antibody level was assessed on day 33 of the induction and day 18 of the reinduction protocols. In the reinduction phase, 24 patients presented an allergic reaction to L-asp, and in these cases blood samples were collected before the dose triggering the hypersensitivity reaction was administered, and these were used for antibody assessment. After hypersensitivity reaction, the L-asp preparation was changed to its pegylated form (Oncaspar, Medac GmbH, Germany). Detailed characteristics of the study group are presented in Table 1.

L-asp activity measurement

L-asp activity was assayed using a colorimetric method described in detail previously [10]. The activity of L-asp was considered adequate when the mean value of all measurements in each phase of treatment exceeded 100 U/l.

Antibody assessment

The antibody assay was based on home ELISA method. On 96-well L-asparaginase (Medac, Germany) -coated plates (Nunc, Denmark) studied serum samples and standard solutions (7.8–500 ng/ml) of anti-L-asp antibodies (Acris Antibodies, Germany) were added and incubated at room temperature for one hour. After the incubation the wells were drained and washed with PBS-Tween20 (SIGMA, USA) three times. Then the wells were developed with 100 μl of horseradish peroxidase-conjugated rabbit anti-human IgG, IgM and IgE antibodies (Dako, Denmark) and incubated at room temperature for one hour. After the incubation the plates were washed three times with PBS-Tween20 and 100 μl of TMB substrate solution (Sigma-Aldrich, USA) was added into each well. The plates were incubated at room temperature in the dark for 15 min. The reaction was stopped by adding 100 μl of 2 M hydrochloric acid. All the determinations were performed in duplicates. Individual wells were read with ELISA MPR96 (Dynamica, Switzerland) at a wavelength of 450 nm. Antibody concentrations were read using a standard curve. The results were referenced to normal values, previously determined in sera collected from thirty-one healthy, untreated volunteers, i.e. a count higher than two standard deviations from the mean value was considered as positive (31.67 μg/mL for IgG, 4.81 μg/mL for IgM and 1.04 μg/mL for IgE).

Clinical symptoms of L-asp hypersensitivity were defined according to Common Terminology Criteria for Adverse Events (CTCAE vol. 4.03) [15].

Statistical analysis

Statistical analysis was performed using Statistica 12.5 (Statsoft, Poland). The medians were compared with the Mann-Whitney *U* test. The differences between timepoints were evaluated using Wilcoxon's rank test. Correlations were assessed with the Spearman test. A *p* value lower than 0.05 was considered statistically significant.

Results

Antibody levels in the induction and reinduction phase

At the end of the first exposure to L-asp, specific anti-L-asparaginase antibodies were detected in 35 patients (54%). In

Table 1
Study group characteristics.

Number of patients:	Total n = 65
-male	n = 33 (51%)
-female	n = 32 (49%)
Risk group	
-SR[a] + IR[b]	n = 55 (85%)
-HR[c]	n = 10 (15%)
Age at diagnosis (median, IQR)	6.5 yrs. (4.5–12.5)
Initial white blood count (n/μL, median; IQR)	6500 (3600–16,000)
Clinical L-asp allergy:	
-induction	0/65
-reinduction	24/55 (43%)
Inadequate L-asp activity:	
-induction	9/65 (14%)
-reinduction	8/55 (14,5%)

[a] SR- Standard Risk.
[b] IR – Intermediate Risk.
[c] HR – High risk.

Table 2
Changes in anti-L-asparaginase antibody concentration during ALL therapy.

	Induction (n = 65)	Reinduction (n = 55)	*p*
IgM (μg/mL; median, *IQR)	2.86 (1.4–5.07)	5.42 (2.87–9.86)	0.0003
IgG (μg/mL; median, *IQR)	9.24 (4.46–32.54)	32.98 (7.12–75.23)	0.003
IgE (μg/mL; median, *IQR)	0.29 (0.22–0.77)	0.69 (0.37–1.1)	0.02
ΔIgM (median, *IQR)	–	1.74 (−0.65–6.1)	–
ΔIgG (median, *IQR)	–	8.54 (−4.29–46.25)	–
ΔIgE (median, *IQR)	–	0.34 (−0.11–0.71)	–

*IQR – interquartile range.

total, 20/65 (31%) patients were positive for IgG, 17/65 (26%) for IgM and 13/65 (20%) for IgE anti-L-asp antibodies. Three patients possessed anti-L-asp antibodies in all three studied classes. In the reinduction phase of the treatment, anti-L-asp antibodies were found in 38/55 patients (69%), and 30 (54%), 28 (51%) and 12 (22%) patients were positive for IgM, IgG and IgE antibodies, respectively. In this phase of the therapy, the number of patients with antibody positivity in all three studied classes increased to six (9%). Changes in anti-L-asp antibody titers during leukemia treatment were statistically significant (Table 2) and are depicted in Fig. 1a-d. In the subgroups of patients with positive anti-L-asp antibodies in induction remission phase of the treatment, the median IgG concentration was 39.56 μg/mL (IQR: 33.0–57.42), median IgM concentration was 7.49 μg/mL (IQR: 5.88–8.87), and median IgE concentration was 1.47 μg/mL (IQR: 1.14–2.33). In the reinduction phase of treatment, in patients with positive antibodies, the median concentration of anti-L-asp antibodies was 68.41 μg/mL for IgG (IQR: 40.49–114.55), 9.50 μg/mL for IgM (IQR: 6.61–12.10), and 2.00 μg/mL for IgE (IQR: 1.31–3.27).

L-asp activity and allergy

No cases of clinical allergy to L-asp were observed during induction remission. Inadequate L-asp activity (L-asparaginase activity below 100 U/l, without clinical hypersensitivity) was noted in nine (14%) patients. In the reinduction phase, clinical allergy was seen in 24/55 (43%) of cases, and inadequate L-asp activity in 8/55 patients (14.5%). During induction remission, median L-asp activity measured as an average of five timepoints per each patient, was found to be 174 U/l (IQR 126–262 U/l). During reinduction, median L-asp activity was found to be 154 U/l (IQR 50–323), being measured in an average of two timepoints per patient.

During induction remission, we found no linear relationship between antibody levels and L-asp activity (Fig. 2a, c, e), however IgM antibodies concentration was significantly higher in patients with inadequate L-asp activity (median 5.88 μg/mL, IQR 2.76–7.91 *versus* 2.81 μg/mL, 1.32–4.43, $p = 0.03$) (Fig. 3a). During reinduction, L-asp activity inversely correlated with anti-L-asp IgM and IgG antibody level (Spearman's R= -0.38 for IgM and -0.51 for IgG) (Fig. 2b and d). Significantly higher levels of IgG were observed in the group of patients with allergic reactions to L-asp (median 61.6 μg/mL, IQR 9.13–142 *versus*18.36 μg/mL, IQR 6.83–38.88, $p = 0.01$) (Fig. 4c). Interestingly, IgE levels were found to be lower in patients with L-asp allergy than in the group without clinical hypersensitivity, although this difference was not statistically significant (median 0.53 μg/mL, IQR 0.23-0.84 *versus* 0.77 μg/mL, 0.52–1.19, $p = 0.07$) (Fig. 4e). Higher IgE levels were noted in patients with inadequate L-asp activity in the reinduction phase (median 0.91 μg/mL, IQR 0.71–1.19 *versus* 0.64 μg/mL, 0.3-0.99, $p = 0.03$) (Fig. 3f).

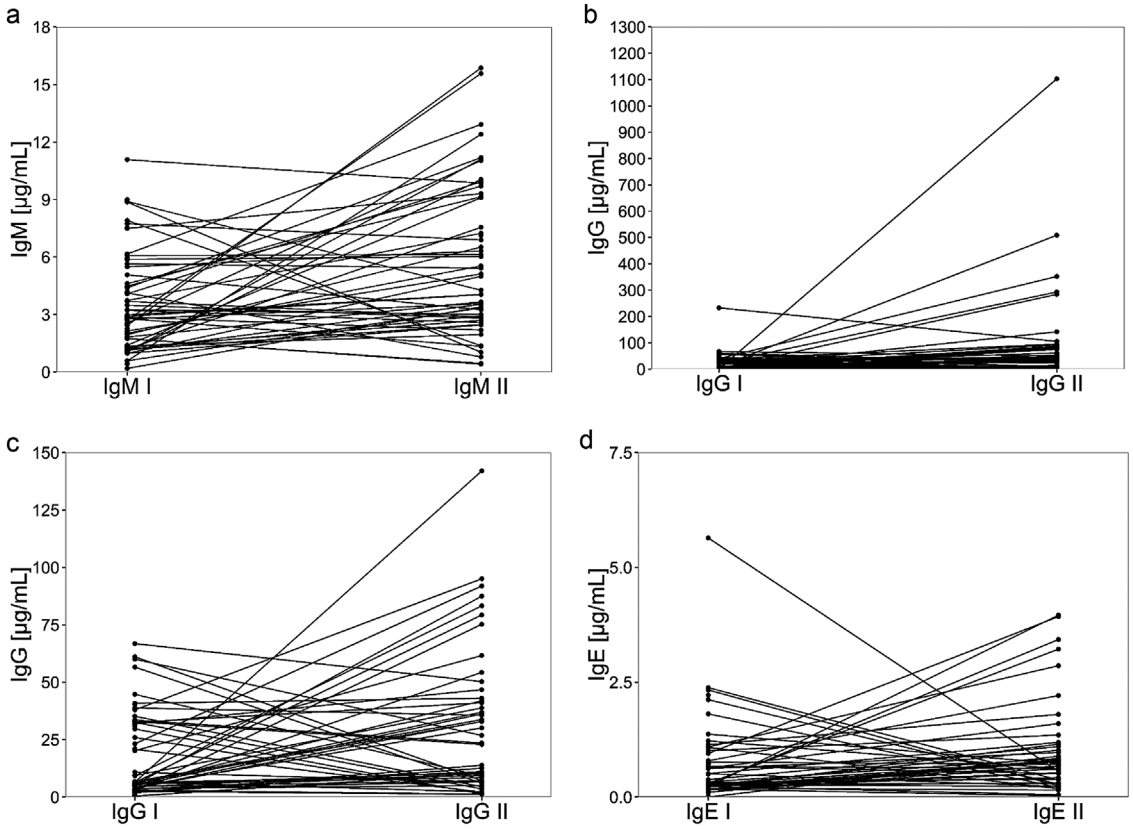

Fig. 1. Changes in anti-L-asparaginase antibody concentrations during the induction (I) and reinduction (II) phases. Panel a – IgM antibodies; panel b – IgG antibodies - range 0–1300 μg/mL; panel c – IgG antibodies - range 0–150 μg/mL; panel d – IgE antibodies.

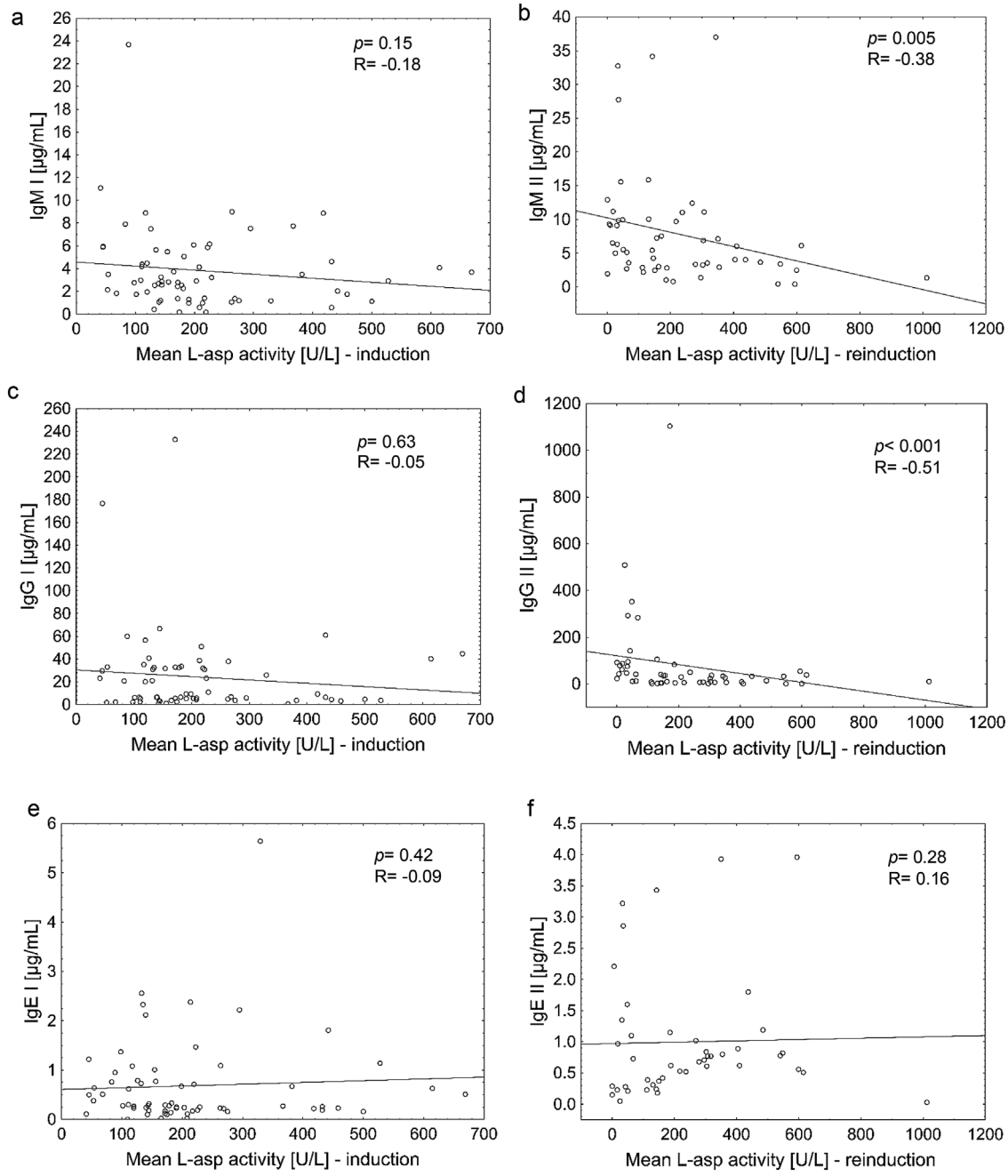

Fig. 2. Correlations between anti-L-asp antibody levels and drug activity in the induction (I) and reinduction (II) phases of the treatment. Panel a – IgM antibodies (I); panel b – IgM antibodies (II); panel c – IgG antibodies (I); panel d – IgG antibodies (II); panel e – IgE antibodies (I); panel f – IgE antibodies (II).

The groups were also compared with regard to the difference in antibody levels between the induction and reinduction phases (Δ Ig). No significant differences were found between groups; however, in patients with inadequate L-asp activity during the induction phase, Δ IgM was lower than in those with L-asp activity over 100 U/l (Fig. 5a).

Discussion

At present, it is possible to cure the great majority of cases of childhood acute lymphoblastic leukemia (ALL). This success can to some extent be attributed to the proper use of L-asp in ALL therapy. It has been shown that the maintenance of sufficiently high activity of the drug for a considerable period of time significantly improves the outcome of pediatric ALL [16]. This effect can be achieved without incurring excessive financial costs and complicated diagnostic procedures. Systematic monitoring of L-asp activity during leukemia treatment is necessary, and nowadays it has become a standard for Polish pediatric oncology departments [17].

The phenomenon of silent inactivation is estimated to occur in about 40% of patients receiving L-asp [5,9]; however the precise working definition of the phenomenon has been evolving. The latest recommendations of the Polish Pediatric Leukemia/Lymphoma Study Group define it as two activity measurements below the detection limit for the method (i.e. 20 U/l) [17]. This strict definition means complete drug inactivation. However, in contrast to Poland, some authors postulate to use a definition based on observations indicating an improvement in patients' outcome, when changes of L-asp formulation are made in the case of drug activity decreasing below 100 U/l in one measurement [17,18]. The

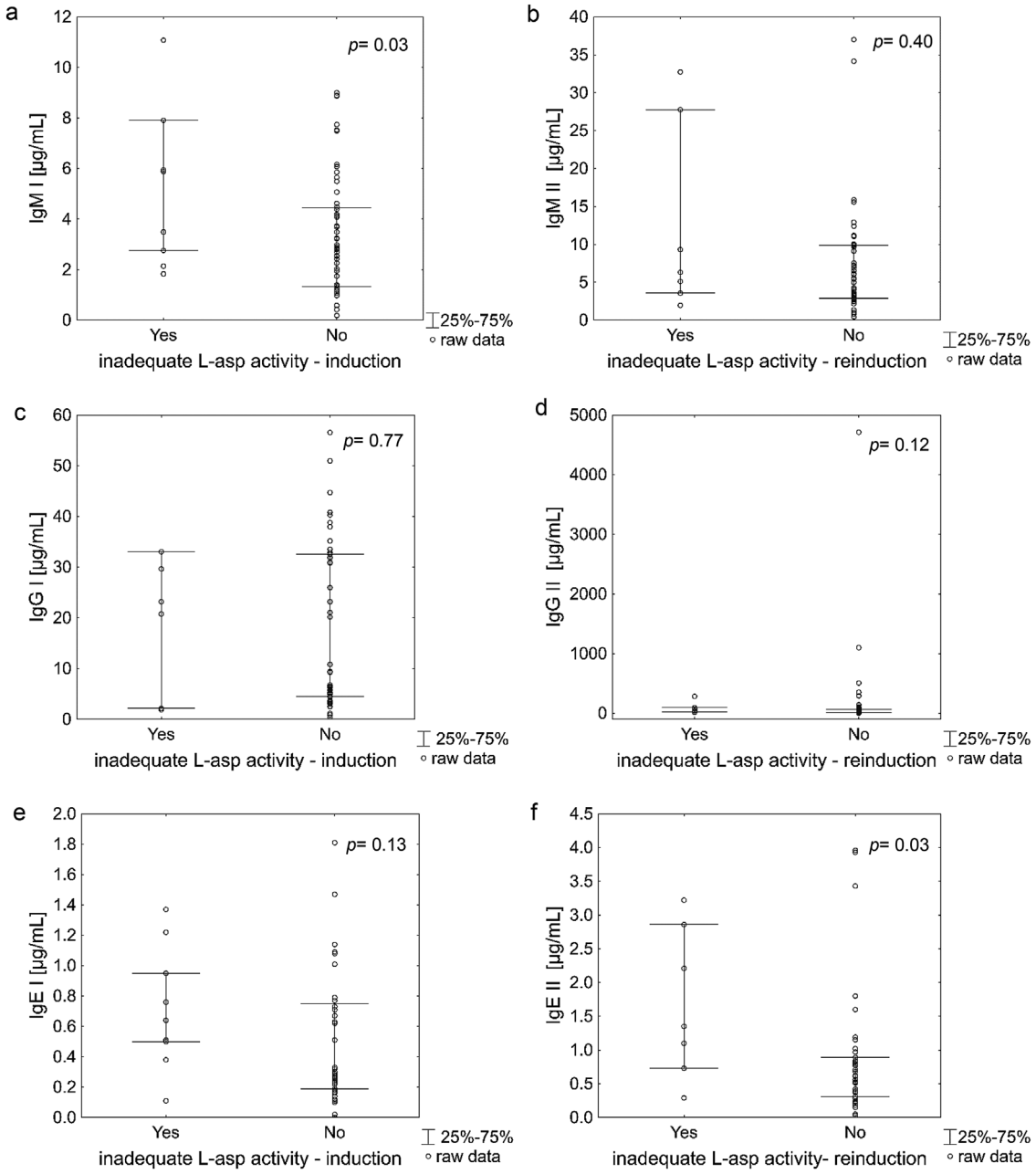

Fig. 3. Associations between antibody levels and inadequate L-asp activity in induction (I) and reinduction (II) remission. Panel a – IgM antibodies (I) ; panel b – IgM antibodies (II); panel c – IgG antibodies (I); panel d – IgG antibodies (II); panel e – IgE antibodies (I); panel f – IgE antibodies (II).

present study uses the term 'inadequate L-asp activity' in order to include all the patients with subtherapeutic L-asp activity (i.e. below clinically relevant level).

Therapeutic ALL protocols adopt varied schedules for the use of L-asparaginase. The drug is typically administered as several doses in a few cycles, with longer or shorter intervals between the cycles. While in the past, most therapeutic L-asp therapy protocols began with the native form of *E. coli* L-asparaginase, most of the leading working groups currently recommend using the pegylated form of L-asp (PEG-asp) as the first line of the treatment. Such a strategy is associated with a lower risk of the development of clinically overt hypersensitivity and reduces the number of patients with anti-L-asp antibodies [7,19]. However, the use of PEG-asp does not completely eliminate the risk of antibody production: in fact, the use of PEG-asp increases the risk of silent inactivation, which means inadequate drug activity without clinical signs of allergy. Such patients can only be recognized *via* systematic monitoring of L-asp activity during the treatment.

While most therapists change the drug formulation, i.e. native *E. coli* to PEG-asparaginase or Erwinase, and PEG-asp to Erwinase, in the case of a clinically overt allergic reaction to L-asp, it is not entirely clear how to proceed in the case of silent inactivation. In addition, there are still reports suggesting that treatment with the same drug may be continued after an allergic reaction, as long as antihistaminics are used [20]; however, this choice of therapy may not be advisable because specific anti-L-asparaginase antibodies inactivate the drug, and this cannot be prevented by antihistaminics. The goal of treatment with asparaginase is to enable and maintain the adequate activity of the drug, rather than supplying all its scheduled doses alone. Moreover, some reports indicate that these specific antibodies may influence other important elements of ALL treatment [21,22].

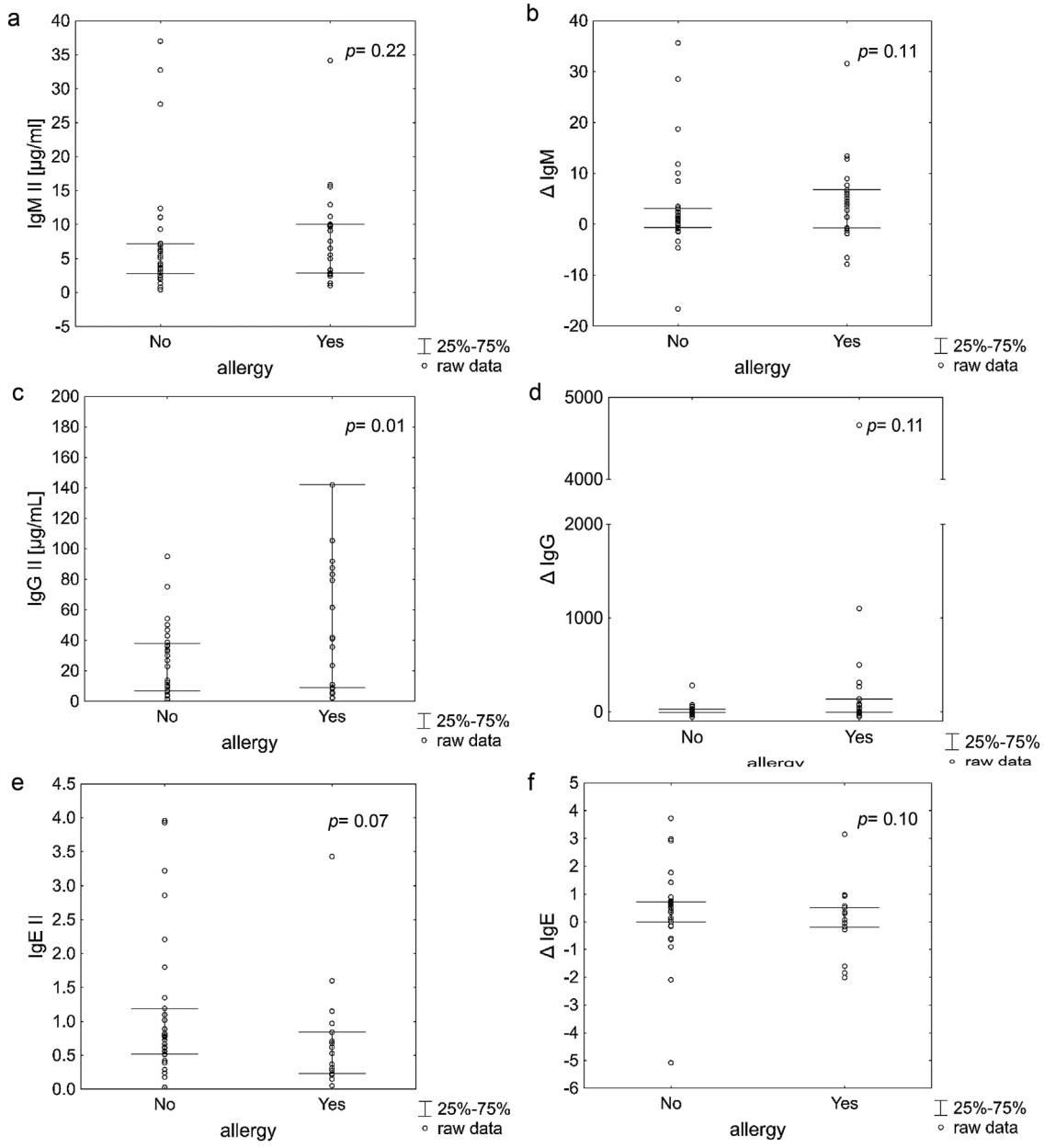

Fig. 4. Anti-L-asp antibodies in L-asp allergy. Panel a – IgM antibodies; panel b - Δ IgM; panel c – IgG antibodies; panel d - Δ IgG; panel e – IgE antibodies; panel f - Δ IgE. As L-asp allergy occurred only in the reinduction, only levels of antibodies in this phase of the treatment were assessed.

It is well known that the risk of both clinically apparent allergic reactions to L-asp and silent inactivation most often appear during re-exposure to the drug. Allergic reactions often have the character of an immediate reaction, during the first minutes of the infusion, usually at the first dose of the new L-asp cycle. Therefore, some authors believe that the allergic reaction to asparaginase mainly depends on IgE antibodies [14]. Other authors postulate that the clinical symptoms of L-asp allergy depend on mediators released from basophils and mast cells in the IgE-dependent mechanism, but inactivation of the drug largely corresponds to IgG antibody level [10]. Our findings indicate that specific anti-L-asparaginase antibodies can be detected in patients even during the first exposure to the drug. In this phase of treatment, a clinically apparent allergic reaction is rare and no such reaction was observed in our cohort. However, even in this phase of treatment, some of our patients demonstrated inadequate L-asp activity, and this was found to be associated with the presence of IgM antibodies. This subgroup also displayed a smaller difference in IgM level between the induction and reinduction phases, which suggests that the elevated IgM level observed in the induction phase did not further increase during reinduction. Whether it is the result of lack of immune stimulation due to drug inactivation, or simply the effect of class switching, cannot be concluded from our study and further studies of the mechanisms of immune response generation towards L-asp in relation to drug activity are needed.

The symptoms of L-asp hypersensitivity range from urticaria to anaphylactic shock and are alleviated by antihistaminics and steroids; as these appear to be related to mast cell activation, it is reasonable to assume that asparaginase-specific IgE are likely to play an important role in L-asp response and clearance. In addition, as the present study also tests the hypothesis that IgE may play a significant role in adverse immunoreactions to asparaginase, it

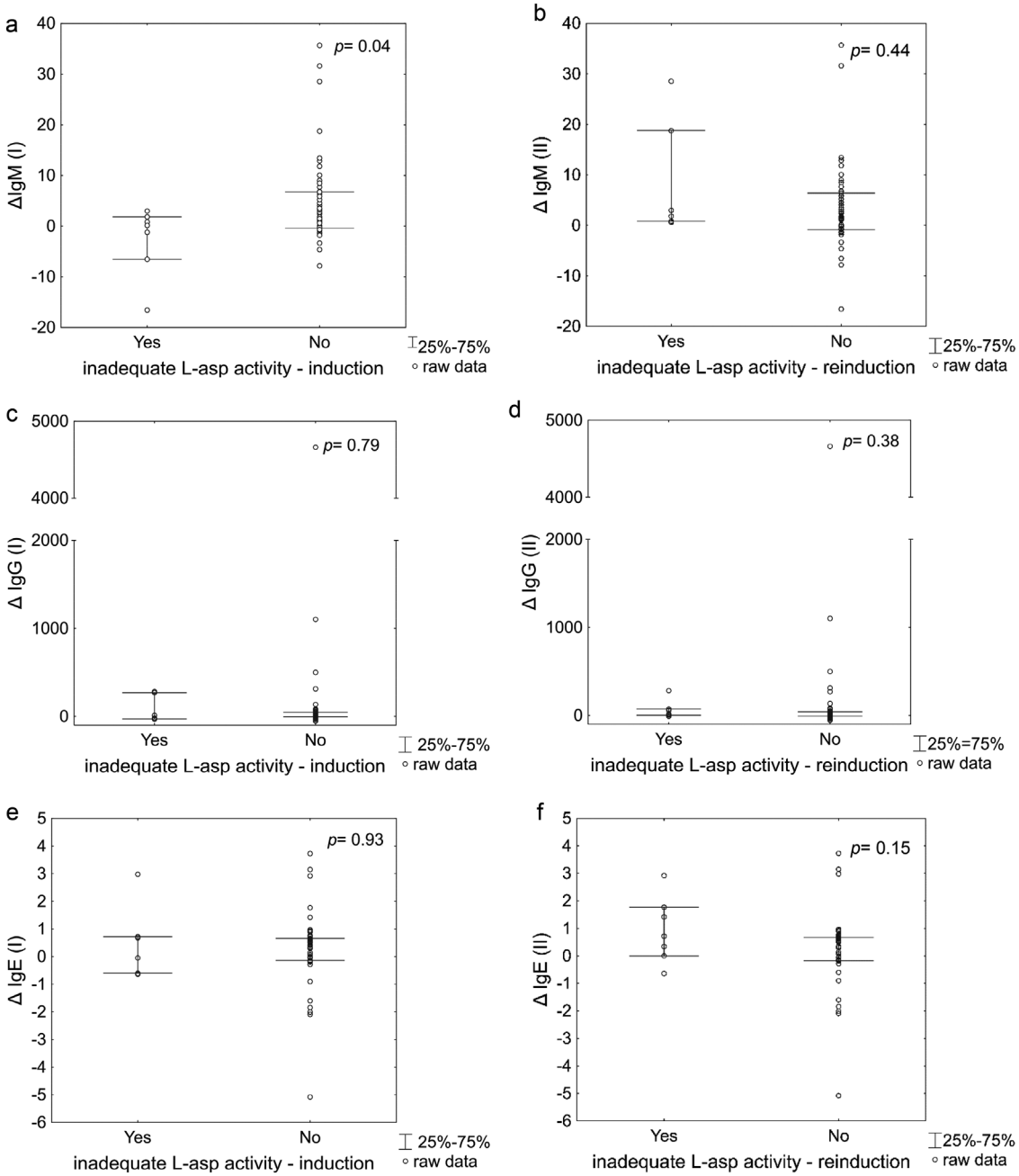

Fig. 5. Associations between changes in antibody levels (Δ Ig) and inadequate L-asp activity in induction (I) and reinduction (II) remission: panel a - Δ IgM (I); panel b - Δ IgM (II); panel c - Δ IgG (I); panel d - Δ IgG (II), panel e - Δ IgE (I); panel f - Δ IgE (II).

examines the importance of IgE in the mechanisms of L-asp hypersensitivity. Somewhat disappointingly, our findings did not identify any relationship between IgE antibodies and clinically overt allergy. Patients with L-asp hypersensitivity demonstrated higher IgG levels in the reinduction phase, whereas the subgroup with inadequate L-asp activity presented higher IgE levels. These results may support the theory by Fabry et al. that L-asparaginase hypersensitivity is primarily independent of IgE level [23]; however, a study based on BAT (basophil activation test) and skin prick tests found that the role of specific IgE cannot be excluded in the course of L-asp allergy [14]. It remains unclear whether these contradictory observations are due to the complexity of the mechanisms of L-asp allergy or the effect of difficulties in determining serum asparaginase-specific IgE. Sole humoral response assessment may be the limitation of our study, as cell-mediated processes may also contribute to L-asp hypersensitivity. Nevertheless, our findings suggest that drug-specific IgE appears to have lower prognostic value than specific IgG and IgM, whose significance has been described previously. Despite the fact that we did not find any linear relationship between IgE antibodies and L-asp activity, it can be noticed that a group with high IgE antibody titers can be seen in the reinduction phase below the clinically relevant drug activity threshold (i.e. < 100 U/l) (Fig. 2, panel f). This observation was confirmed when patients were analyzed according to their L-asp activity status (Fig. 3, panel f).

Low L-asp activity without the presence of antibodies implicates the existence of an alternative non-immunological mechanism influencing drug activity, one of which may be the proteolytic degradation of L-asp, which was first described *in vitro* and later confirmed by clinical observation [24,25]. The present

study assessed merely the humoral response to L-asp; a full insight into the process of L-asp hypersensitivity might be achieved by assessing the other elements of the immune response, such as antigen-specific lymphocytes; however few, if any, such studies in this area have been published so far. Majority of studies assessing immune response to L-asp evaluate only IgG antibodies, since this class of immunoglobulins has been demonstrated to be of the greatest importance for L-asp activity.

To conclude, our findings indicate that immune-mediated L-asp inactivation and hypersensitivity is a complex phenomenon, and it cannot be attributed to the development of a specific class of anti-L-asp antibodies. Although IgG antibodies seem to play a key role in the humoral response to L-asp, it was observed that IgM and IgE immunoglobulins may also influence L-asp activity. Although the extent to which the results obtained with native *E.coli* L-asp correspond to PEG-asparaginase therapy remains to be established, it has been previously found that anti-L-asp antibodies have a high degree of cross-reactivity against different drug formulations [26]. Therefore, from the clinical point of view, monitoring of L-asp activity remains a vital part of the therapy, and is even more important than detecting anti-L-asp antibodies alone.

Conclusion

Subsequent exposures to L-asp in the induction and reinduction phases of the treatment of acute lymphoblastic leukemia were associated with the increase of anti-L-asp antibodies in all studied classes. IgM and IgG anti-L-asp antibody concentrations correlated significantly with L-asp activity in the reinduction phase. Patients with L-asp allergy tended to have higher IgG immunoglobulin levels, whereas those with inadequate drug activity demonstrated higher IgM in the induction and IgE in the reinduction phases of the therapy. The lack of any clear relationship between changes in anti-L-asp antibody profile and L-asp hypersensitivity and inactivation suggests a more complex mechanism behind these phenomena.

Conflict of interest declaration

Dr. Walenciak reports grant from Medical University of Lodz (Young Scientist' Support, Project No. 502-03-1-090-01-502-14-194) during the conduct of the study.

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Author contributions

Study design – MW and Z-SB, data collection – WJ, WK, statistical analysis – JS, WJ, MW, data interpretation – WJ, JS, Z-SB, MW, acceptance of final manuscript version – WJ, JS, WK, Z-SB, MW, literature search – WK, SJ, Z-SB, funds collection – MW, Z-SB.

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